Human Biological Specimens in Research

1. **PURPOSE:** To establish a Research Service policy, outlining the use and review of human biological specimens (HBS) in research. HBS are essential for biomedical research. Federal oversight of collection and use of these materials is mandated in DHHS regulations [45CFR46]. The primary risk in using HBS is the harm that can occur when private information about individual subjects is revealed. Therefore, it is necessary to develop a system of protections to ensure that the risk of breach of confidentiality is minimized and the interests of the persons who provide biologic samples are protected.

2. **POLICY:** The National Bioethics Advisory Commission (NBAC) was appointed to review the practices and policies regarding use of human biologic material in research and to make recommendations for the ethical conduct of these studies. The Veteran Affairs Office of Research & Development, VHA Directive, 2000-043, "Banking of Human Research Subject's Specimens," requires that HBS, as well as the linked clinical data collected as part of research projects conducted by VA investigators in VA facilities or approved off-site locations, are maintained at VA approved tissue banks. The NBAC's draft standards for use of HBS for research were published in 1999. In addition, the Oregon legislature has established laws [ORS 192.531-549; the Genetic Privacy Act] intended to protect the rights of humans who provide HBS for genetic research and to protect subjects from being involved in genetic research against their wishes. Finally, the Heath Insurance Portability & Accountability Act (HIPAA), which became effective April 14, 2003, provides strong protections for the access to, and use and disclosure of, protected health information (PHI). Because the majority of studies involving HBS will eventually involve genetic testing and the creation and use of genetic PHI, the PVAMC policy for the use of HBS is based on the VHA Directive, NBAC guidelines for tissue use, the Oregon Genetic Privacy Law and the HIPAA Privacy Standards.

3. **RESPONSIBILITIES:**

   a. The **Associate Chief of Staff for Research & Development** is responsible for developing and managing policies and procedures involving the use and review of HBS in research.

   b. The **Research and Development Committee (R&D)** is responsible for reviewing research projects involving HBS in accordance with this policy.

   c. The **Institutional Review Board (IRB)** is responsible for reviewing research projects involving HBS in accordance with this policy.

   d. **Principal Investigators (PI)** are responsible for ensuring that their research projects involving HBS are conducted in accordance with this policy.

4. **DEFINITIONS:**

   Note: this section incorporates definitions from Oregon Administrative Rules (OAR 333-025-0100).

a. **Anonymous research:** Scientific or medical research conducted in such a manner that the identity of an individual who has provided a sample, or the identity of an individual from whom genetic information has been obtained, or the identity of the individual's blood relatives cannot be determined. "Anonymous research" does not include research conducted in such a manner that the identity of such an individual, or the identity of the individual's blood relatives, can be determined by the use of a code, encryption key or other means of linking the information to a specific individual.

b. **Blanket informed consent:** The individual has consented to the use of his/her DNA sample or health information for any future research, but the individual has not been provided with a description of, or consented to the use of, the sample in genetic research or any specific genetic research project.

c. **De-identified Information:** De-identified information is health information that does not identify an individual and with respect to which there is no reasonable basis to believe that the information can be used to identify an individual. In order to be considered de-identified, the following 18 elements must be removed: names; geographic subdivisions smaller than a state; zip codes; dates directly related to an individual; telephone numbers; fax numbers; electronic mail addresses; social security numbers; medical record numbers; health plan beneficiary identifiers; account numbers; certificate/license numbers; vehicle identifiers and serial numbers, including license plate numbers; device identifiers and serial numbers; web universal resource locators (URL); internet protocol (IP) address numbers; biometric identifiers, including finger and voice prints; full face photographic images; and any other number, characteristic or code that could be used to identify the individual. Information may also be statistically de-identified.

d. **DNA:** deoxyribonucleic acid.

e. **DNA sample:** Any human biological specimen that is obtained or retained for the purpose of extracting and analyzing the individual's DNA to perform a genetic test. "DNA sample" includes DNA extracted from the specimen.

f. **Genetic characteristic:** A gene, chromosome or alteration thereof that may be tested to determine the existence of or risk for acquiring a disease, disorder, trait, propensity or syndrome, or to identify an individual or a blood relative. "Genetic characteristic" does not include family history or a genetically transmitted characteristic whose existence or identity is determined by means other than through a genetic test.

g. **Genetic information:** Information about an individual or the individual's blood relatives obtained from a genetic test.

h. **Genetic research:** Research using human DNA samples, genetic testing or genetic information.

i. **Genetic test:** A test for determining the presence or absence of genetic characteristics in a human individual or the individual's blood relatives, including tests of nucleic acids, such as

DNA, RNA, and mitochondrial DNA, chromosomes or proteins in order to diagnose or determine a genetic characteristic.

j. **Human Biological Specimen (HBS):** is defined in the VHA Directive 2000-043 as "any material derived from human subjects, such as blood, urine, tissues, organs, hair, nail clippings, or any other cells or fluids, whether collected for research purposes or as residual specimens from diagnostic, therapeutic, or surgical procedures.

k. **Identification of samples:** Three levels of identification of research samples are recognized. These are differentiated by the amount of information that is available about the subject from whom the sample was obtained. The levels include the following:
   (1) **Unidentified samples (anonymous or de-identified):** Samples that have either been acquired without any identification that may link the data or specimen to a specific subject or for which all identifiers or codes have been removed and destroyed. Please also see the definition for de-identified information.
   (2) **Coded samples:** Samples labeled with a code rather than a name or other personal identifier. When such samples are obtained from a tissue repository, the repository usually retains information that links the code to a particular individual.
   Using this information, the investigator, the repository or a third party could determine which particular person or small group of identifiable individuals provided the biological specimen. Depending on the nature of the identifiers that are associated with a specimen, the sample may or may not meet the definition of a "limited data set" as provided by HIPAA. The IRB will make this determination and also determine if the use of the sample, as specified in the protocol, requires a data use agreement, tracking of disclosures, or business associate agreement. Note that for genetic research, the sample must meet the definition of limited data set in order to qualify as coded under the Oregon Genetic Privacy Law (ORS 192.547) (see section III-D).
   (3) **Identified samples:** Samples collected and supplied to investigators with personal identifiers sufficient to allow identification of the person who provided the material.

l. **Identifiers:** Examples of identifiers include name, Social Security number, hospital number or other unique identifier. Using current information technology, a combination of descriptive data may be sufficient to allow identification of the person who provided the biological specimen and collectively may be considered an identifier (e.g., Zip code, birth date and profession are often sufficient to identify a specific individual).

m. **Limited Data Set:** A limited data set is information that is minimally identified by including a few selected identifiers. The limited data set may only contain: the subject's dates of admission and/or discharge, their date of death (if applicable), their date of birth (which can only be used as necessary), and the subject's five digit zip code or any other geographic subdivision (e.g., state, city, county.). Because a limited data set is not fully de-identified and could potentially be used to re-identify an individual, it is still subject to HIPAA.

n. **Recontact:** Disclosure of genetic research findings to a research subject or the subject's health care provider.

o. **Repository:** A repository is a storage site for collections of HBS available for study. This may be one geographic location or may be a virtual aggregation of biologic specimens from many locations. Repositories are also referred to as tissue banks, collections, resources or inventories, or by other terms.

p. **Sample:** The term sample refers to a portion of the HBS supplied to investigators.

q. **Specific informed consent and authorization for genetic research:** The individual or the individual's representative has consented to, and authorized the use of, that individual's DNA sample or genetic information for genetic research or for a specified genetic research project. The elements of "specific informed consent" and "authorization" are set forth in the Federal Common Rule (45 CFR46.116 –46.118) and HIPAA.

r. **Stored or "banked" Specimen**: specimens collected and stored for future research purposes are considered "banked" specimens.

s. **VA-sponsored tissue bank:** a tissue repository or storage facility at a VA facility or approved off-site location that operates in accordance with VA regulations. It contains HBS collected under VA-approved research protocols that are under both VA ownership and VA control.

t. **VA-approved tissue bank**: differs from a VA-sponsored tissue bank in that an approved tissue bank is located at a non-VA facility and has the appropriate approval from the Chief Research & Development Officer. It must also meet safeguards similar to those required for a VA-sponsored tissue bank. Non-VA sites that may not be acceptable include non-academic, for profit institutions, such as pharmaceutical companies.

u. **Waiver of Consent and Authorization:** This is a request from the investigator to access, use and disclose existing Protected Health Information (PHI) including genetic PHI, without consent and authorization from the subject. This request must be completed and submitted to the VA IRB on the appropriate Portland VA Medical Center (PVAMC) form.

5. **PROCEDURES:**

a. **Required Research Project Information:** All applicable IRB and R&D Committee policies and procedures apply to research involving HBS. All research projects submitted for review by the IRB should include the following information:

(1) **Information on Research Design:** Indicate the importance of the research, the rationale for testing, and the general nature of tests that will be done on the samples.

(2) **Source and retention of samples:** Indicate how samples have been or will be obtained. If identified or coded samples will be obtained from a repository, the investigator should include in the application a copy of the consent form used to collect the original samples and the repository's written procedures for storing and releasing samples. Indicate how long samples will be stored (if the intent is to store as long as possible, so state), and indicate what will happen to samples at the conclusion of the storage period. Note that under the Oregon Genetic Privacy Law (ORS 192.537), DNA samples and genetic information may not be retained without consent or authorization, unless for anonymous research conducted after notification as discussed in Section 5.a.(3) below.

(3) **Consent and authorization procedures:** Whether previously stored samples can be used without additional informed consent and authorization depends on the date on which the

samples were collected, the original consent form used, whether or not samples can be linked to individual subjects, and whether or not any genetic research is proposed. An investigator who requests use of existing specimens may complete the Request for Waiver of Informed Consent and Authorization form.

HBS or genetic information obtained on or after June 25, 2001, may be used without consent in genetic research only if the sample is anonymous, and only if, prior to the time the research is conducted, the subject was notified that anonymous research might take place in the future and, at the time notification took place, the subject did not request that the sample or information be withheld from anonymous research (ORS 192.531-549).

Requirements for samples or information obtained prior to June 25, 2001, are less restrictive under the Oregon Genetic Privacy law, regardless of whether genetic research is involved. For these samples, the IRB may, at its discretion, grant a waiver of additional consent and authorization, depending on whether subjects were originally informed of the possibility of future research, or if the conditions for Waiver of Consent and Authorization given at 45 CFR 46.116(d) and according to HIPAA are met, even if samples are coded or identified.

(4) **Minimization of risk and protection of confidentiality:** Indicate whether samples will be anonymous, coded or identified. If samples are anonymous or coded, specify the process by which they will be anonymous or coded. Describe the security measures that will be used to protect against a loss of confidentiality (note that it is the principal investigator's responsibility to instruct research staff of these security measures to maintain confidentiality). Indicate which individuals will have access to the information, including code-breaking lists, if any.

(5) For genetic research, **additional requirements** under the law for coded research (ORS 192.547) apply and include:

(a) The code is:
   i. Not derived from individual identifiers;
   ii. Kept securely and separately from the DNA samples and genetic information; and
   iii. Not accessible to the investigator unless specifically approved by the IRB.

(b) Data is stored securely in password protected electronic files or by other means with access limited to necessary personnel.

(c) The data is limited to elements required for analysis and meets the criteria in 45C.F.R 164.514(e) for a limited data set.

If identified material is de-identified for use, it will not be possible to relay research results back to subject. While this will protect confidentiality, it may also place the subject at risk for failing to get information about a treatable health condition, and this risk should also be considered. If samples or information will be relayed outside of the VA, indicate under what circumstances and what identifiers, if any, the relayed samples or information will bear. Note that transfer of samples to other researchers with identifiers is strongly discouraged. Obtaining a Certificate of Confidentiality may offer additional confidentiality protections of human repository specimens and data. Depending upon the reason for relaying genetic PHI outside of VA and the type of identifiers attached to the PHI, a data use agreement or business associate agreement may be required.

(6) **Contact with subjects:** If the investigator wishes to contact the relatives of a subject, the investigator must ask the subject to contact his/her relatives in order to seek their permission.

If the subject declines to contact relatives, or the relatives decline contact by the investigator, no contact may occur. If permission is granted for contact, the informed consent and authorization process must be repeated with each relative. Note: this does not apply to the use of anonymous specimens because subjects will not be able to be contacted by virtue of being anonymous specimens.

(7) **Recontact with subjects:** Recontact of a research subject or a patient from whom samples or information was obtained originally for clinical purposes should not occur unless the subject was informed during the initial treatment or research consent and authorization process, that recontact may occur under specified circumstances. Reasons for recontacting research subjects can include recontact for release of clinically relevant research results. If this is desired, precautions must be taken both to minimize the potential harm to subjects of receiving bad news and to guard against the unintended release of the information. The precautions needed in conveying genetic testing results depend on the age at onset of the disorder, the burden of illness, and the availability of treatment or prevention. The communication of genetic information carries with it the responsibility to interpret the results and provide care for the individual; and, thus, it is ideally done in the setting of a clinical rather than research relationship with the subject. Because of the complexity of the results of most genetic tests, subjects cannot be required to inform relatives of the results of the research. The IRB may consider allowing recontact for the purposes of disclosing research results if the following conditions are met: 1) the findings are scientifically valid and confirmed (and where relevant the laboratory producing the results is Clinical Laboratory Improvement Amendments (CLIA) certified), 2) the findings have significant implications for the subject's or the public's health, and 3) a course of action to ameliorate or treat the subject's or the public's health concerns is readily available. In the event these conditions are met, the results may only be released to the subject or any other party with the subject's permission, and appropriate medical advice and referral must be provided (OAR 333-025-0130). Note: this does not apply to the use of anonymous specimens.

(8) **Withdrawal:** HBS or information that are labeled in such a way that the subject from which the HBS or information was obtained can be identified must be destroyed upon request, regardless of whether the HBS or information are currently being used in an ongoing research project. The researcher has the option of removing all identifiers from the HBS or information and continuing to use them, but only if the subject is informed of this intent during the consent and authorization process. Note: this does not apply to the use of anonymous HBS.

b. **Level of Review Required**

(1) Research involving identified or coded HBS will generally be reviewed by the convened IRB.

(2) The expedited review process is available for research involving HBS if the research involves only minimal risk and is also limited to one of the categories specified in the Federal Register, 63 FR 60364-60367. However, the financial, psychological and social risks of genetic studies may prevent them from meeting the minimal risk criterion for expedited review, and these factors will be carefully considered prior to granting an expedited review.

(3) Exemption from IRB oversight can only be granted for genetic studies if samples are anonymous, pre-existing, and meet notification requirements as stated in the previous section. The studies must meet the Federal requirements specified at 38CFR16.101 (b)(1-6).

c. **Consent and Authorization Requirements**

(1) Elements of the consent and authorization process may be waived or modified by the IRB under some circumstances as defined by VA regulations, 45CFR46, HIPAA and Oregon state law. In general, prospective collection of coded or identified samples must be done using written consent and authorization. General consent statements given in conjunction with consent for a clinical or surgical procedure may not be presumed to cover research use of specimens unless research use, including genetic testing, is specifically listed as a possibility.

(2) Investigators must retain signed consent/authorization forms, but these should not be stored in a way that could identify an otherwise unidentified sample.

(3) In addition to the standard elements of consent and authorization required for all research involving human subjects, the following elements must be included in the ICF when HBS will be used as indicated in the IRB SOP.

(a) If the researchers believe that the bodily fluids, substances or tissues of a research subject could be part of or lead to the development of a commercially valuable product, the following verbatim statement is required: "By consenting to participate, I authorize the use of my bodily fluids, substances, or tissues."

(b) Statement of whether or not the specimen will be used for future research and allow the choice of how the specimen will be used (any research, research by the PI, or other researchers, genetic analysis, research related to specific area, etc.).

(c) Whether or not the research results of future use of the HBS will be conveyed to the subject.

(d) Whether or not the subject will be re-contacted after the original study is completed.

(e) If the subject requests, the specimen and all links to the clinical data will be destroyed.

(4) **Waiver of written consent and authorization**: Federal regulations permit the IRB to waive the requirement to obtain documented informed consent and authorization for some categories of research, and some types of research involving HBS fall into these categories. Note, however, additional restrictions apply for genetic research as discussed in previous sections. The use or disclosure of PHI must involve no more than minimal risk to subjects'. Also, the IRB will not waive consent and authorization when release of information to the subject or their health care provider is considered likely. For existing coded or identifiable samples (those already collected and stored), the NBAC recommends that IRBs consider research to be of minimal risk if the study adequately protects the confidentiality of the personally identifiable information associated with the sample. The request for Waiver of Consent and Authorization is available on the R&D Service website: http://www.va.gov/portlandrd/pages/support/award/form.htm#irb

c. If a research project requires that the HBS be analyzed/used at a non-VA institution, a written understanding between the VA investigator and the non-VA institution must specify the analysis/use as defined in the protocol. The agreement must also specify that any remaining quantities of the HBS shall be either destroyed or returned to the VA. If the remaining quantity is destroyed, that institution must certify the destruction of the HBS in writing. The remaining quantity may not be retained and/or stored by the non-VA institution. A template

Memorandum of Understanding between the VA investigator and the non-VA institution that specifies the following is available on the R&D Service website: http://www.va.gov/portlandrd/pages/support/award/form.htm#irb.

6. GUIDELINES FOR REPOSITORIES

a. A repository that is utilized for human subjects research should have written procedures for procuring (including recruitment, and informed consent and authorization processes) and storing HBS, determining who will have access to HBS, and protecting personally identifiable information. All research protocols aimed at setting up repositories of HBS must be submitted to the IRB for review and approval prior to collecting HBS.

b. HBS maintained in a repository may only be released to collaborators who are both competent researchers and knowledgeable in the legal and ethical issues involved in confidentiality and consent and authorization in human research, regardless of whether the researchers are located at PVAMC or elsewhere. Samples from repositories at PVAMC should not be provided to non-PVAMC investigators without written documentation of local IRB approval, or documentation from the local IRB indicating that the protocol is exempt from review.

c. For IRB approved research protocols that collect, use or store HBS, the HBS must be stored in either a VA-sponsored or VA-approved tissue bank. All tissue banks sponsored by the National Cancer Institute and National Institute on Drug Abuse (NIDA) Center for Genetic Studies are considered VA approved tissue banks. Non-VA sites that may not be acceptable as tissue banks include non-academic, for profit institutions, such as pharmaceutical companies.
   (1) If a tissue bank does not fit the criteria of a VA-sponsored of VA-approved tissue bank, then the tissue bank must be approved by the Chief Research & Development Officer, VA Central Office, prior to final study approval and initiation. In order to request approval, specific questions and statements must be addressed. Please refer to the guidance, "Required Information for Requesting Approval of a Non-VA or Non-National Cancer Institute Tissue Bank," available on the R&D Service website: http://www.va.gov/portlandrd/pages/support/award/form.htm#irb

d. Depending on the nature of the information that is released with a sample, a data use agreement or business associate agreement may be required. The IRB approval will indicate if one of these additional agreements is necessary.

e. Use of samples from a repository must be restricted to the stipulations indicated in the original consent/authorization form used to procure the specimen, unless the sample is studied anonymously.

f. Investigators must obtain approval from the PVAMC IRB and R&D Committee when samples from repositories will be studied at PVAMC or when PVAMC employees are co-investigators, regardless of the location of the repository. IRB and R&D Committee review and approval must be complete before samples are released for use.

g. Investigators and repositories must maintain records to assure compliance with any specified restrictions of sample use, including any restrictions placed by the person providing the

specimen. Investigators receiving samples with identifiers or codes are legally and ethically responsible for maintaining the confidentiality of the subjects and for complying with all HIPAA requirements and the Oregon Genetic Privacy Law, 192.531-549, when applicable.

7. **USE OF PRE-EXISTING COLLECTIONS**

a. Specimens collected, tested and/or stored solely for clinical care of a specific patient are not considered part of research and are not covered by this policy. However, if an investigator wishes to use specimens originally collected for clinical purposes for research purposes, that activity is covered by this policy and IRB and R&D Committee review is required.

b. Many existing collections of human biologic specimens were begun before guidelines for research involving human biologic specimens were developed. Many of these specimens may have been obtained without consent or with only general clinical consent, and recontacting the individuals who provided the specimens may be difficult or impossible. In such situations, investigators should either submit an application to the IRB for a Waiver of Consent and Authorization, or should adopt a policy to de-identify their collection.

8. **REFERENCES:** VHA Directive 2000-043 Banking of Human Research Subjects' Specimens, November 6, 2000
Oregon Genetic Privacy Law, 192.531-549
National Bioethics Advisory Commission (NBAC), Draft Standards 1999
PVAMC Institutional Review Board, Standard Operating Procedures

9. **CONCURRENCES:** Endorsed by the Research & Development Committee 08/30/2004

10. **RESCISSION:** None

11. **FOLLOW-UP RESPONSIBILITY:** ACOS, Research & Development Service (R&D)

Michael P. Davey, M.D., Ph.D.
ACOS, Research & Development Service